10-7-2020

Retrospective evaluation of the safety and tolerability of pimobendan in cats with obstructive vs nonobstructive cardiomyopathy

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Abstract

Background Pimobendan is frequently used off-label for treatments of cats with congestive heart failure (CHF). Concern exists regarding the safety of pimobendan in cats with outflow tract obstruction (OTO).

Objectives In cats treated with pimobendan, incidence of adverse effects will not differ between cats with OTO vs cats with nonobstructive cardiomyopathy.

Animals Two-hundred sixty cats with CHF (57 with OTO, 203 with nonobstructive disease).

Methods Retrospective medical record review. Groups were compared using 2-sample t-tests, Wilcoxon rank-sum tests, and Fisher exact tests.

Results Compared to cats with nonobstructive cardiomyopathy, cats with OTO were younger (8.9 [interquartile range (IQR) 6.6] vs 10.8 [6.3] years, P = .0036), more likely to have a heart murmur (51/57 [90%] vs 76/203 [37.8%] cats, P < .0001), more likely to manifest CHF as pulmonary edema (53/57 [83%] vs 144/203 [70.9%] cats, P = .0004), and less likely to have pleural effusion (19/57 [33%] vs 122/203 [60.1%] cats, P = .0005). Adverse effects suspected to be related to pimobendan administration occurred in 12/260 cats (4.6%), including 11/203 cats (5.4%) with nonobstructive cardiomyopathy and 1/57 cat (2%) with OTO (P = .7). Pimobendan was discontinued due to adverse effects in 4/260 cats (1.5%), 3 with nonobstructive disease and 1 with OTO (P = 1.0). Acute adverse hemodynamic effects after pimobendan administration were not detected in any cats.

Conclusions and Clinical Importance Pimobendan is well tolerated in cats with cardiomyopathy and CHF, regardless of the presence of OTO.

Disciplines

Small or Companion Animal Medicine

Comments

This is the published version of the following article: Ward, Jessica L., Efrem Z. Kussin, Melissa A. Tropf, Sandra P. Tou, Teresa C. DeFrancesco, and Bruce W. Keene. "Retrospective evaluation of the safety and tolerability of pimobendan in cats with obstructive vs nonobstructive cardiomyopathy." *Journal of Veterinary Internal Medicine*. DOI: 10.1111/jvim.15920. Posted with permission.

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STANDARD ARTICLE

Journal of Veterinary Internal Medicine ACVIM

American College of
Veterinary Internal Medicine

Retrospective evaluation of the safety and tolerability of pimobendan in cats with obstructive vs nonobstructive cardiomyopathy

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Background: Pimobendan is frequently used off-label for treatments of cats with congestive heart failure (CHF). Concern exists regarding the safety of pimobendan in cats with outflow tract obstruction (OTO).

Objectives: In cats treated with pimobendan, incidence of adverse effects will not differ between cats with OTO vs cats with nonobstructive cardiomyopathy.

Animals: Two-hundred sixty cats with CHF (57 with OTO, 203 with nonobstructive disease).

Methods: Retrospective medical record review. Groups were compared using 2-sample t-tests, Wilcoxon rank-sum tests, and Fisher exact tests.

Results: Compared to cats with nonobstructive cardiomyopathy, cats with OTO were younger (8.9 [interquartile range (IQR) 6.6] vs 10.8 [6.3] years, P = .0036), more likely to have a heart murmur (51/57 [90%] vs 76/203 [37.8%] cats, P < .0001), more likely to manifest CHF as pulmonary edema (53/57 [83%] vs 144/203 [70.9%] cats, P = .0004), and less likely to have pleural effusion (19/57 [33%] vs 122/203 [60.1%] cats, P = .0005). Adverse effects suspected to be related to pimobendan administration occurred in 12/260 cats (4.6%), including 11/203 cats (5.4%) with nonobstructive cardiomyopathy and 1/57 cat (2%) with OTO (P = .7). Pimobendan was discontinued due to adverse effects in 4/260 cats (1.5%), 3 with nonobstructive disease and 1 with OTO (P = 1.0). Acute adverse hemodynamic effects after pimobendan administration were not detected in any cats.

Conclusions and Clinical Importance: Pimobendan is well tolerated in cats with cardiomyopathy and CHF, regardless of the presence of OTO.

Abbreviations: ATE, arterial thromboembolism; CHF, congestive heart failure; DCM, dilated cardiomyopathy; DMVD, degenerative mitral valve disease; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; IRIS, International Renal Interest Society; LA, left atrium/atrial; LV, left ventricle/ventricular; OTO, outflow tract obstruction; RCM, restrictive cardiomyopathy.

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1 | INTRODUCTION

Pimobendan, a combined positive inotrope (calcium sensitizer) and vasodilator (phosphodiesterase-III inhibitor), has become the standard of care for dogs with advanced heart disease. This drug confers survival benefit in dogs with congestive heart failure (CHF) secondary to dilated cardiomyopathy (DCM)[1,2] and degenerative mitral valve disease (DMVD),[3] as well as benefit in delaying onset of CHF in dogs with preclinical DCM[4] and advanced preclinical DMVD.[5]

No consensus exists about off-label use of pimobendan in cats with CHF.[6] The most common cause of CHF in cats is hypertrophic cardiomyopathy (HCM), a disease of primarily diastolic dysfunction for which positive inotrope treatment might appear counterintuitive.[6,7] In cats with hypertrophic obstructive cardiomyopathy (HOCM), pimobendan could be contraindicated because increased contractility could worsen the degree of dynamic left ventricular (LV) outflow tract obstruction (OTO).[8,9] However, biventricular longitudinal systolic dysfunction is a feature of HCM in cats,[10,11] suggesting that positive inotropy could confer therapeutic benefit. Other potential ancillary benefits of using pimobendan in cats with HCM include positive lusitropy, improved left atrial (LA) function, balanced vasodilation, increased renal blood flow, and adjunctive anticytokine and antiplatelet effects.[12,13]

Published literature regarding safety and efficacy of pimobendan in cats is relatively sparse, particularly in the subpopulation of cats with OTO. Based on several retrospective studies of cats with CHF and LV systolic dysfunction, pimobendan is well tolerated.[12,14,15] A total of 229 cats were evaluated across these studies, including 4 cats with HOCM, none of which had adverse effects of pimobendan. A single cat with multiple congenital cardiac defects (including an OTO) developed hypotension after receiving pimobendan, which resolved with discontinuation of the drug.[12]

More recently, a retrospective case-control study of 54 cats with CHF and normal systolic function included 5 cats with HOCM, which received pimobendan, none of which had adverse effects.[16] A subsequent prospective placebo-controlled study of pimobendan in 82 cats with CHF included 27 cats with HOCM, none of which had adverse effects of pimobendan.[17] In a laboratory setting involving 13 research colony cats with familial HCM or HOCM, a single oral dose of pimobendan does not increase LV outflow velocity or likelihood of LV OTO compared to placebo,[13] challenging the specific concern that pimobendan worsens OTO in cats with HOCM.

Based on published evidence and clinical experience, some veterinary cardiologists currently administer pimobendan to cats as part of routine treatment of CHF regardless of the presence of OTO. Other cardiologists remain concerned about the safety of pimobendan in cats with OTO, particularly given the small total number of cats with HOCM receiving pimobendan in published studies. The purpose of

the present study was to describe safety and tolerability of pimobendan administered to cats with cardiomyopathy and CHF, and particularly to compare results between cats with obstructive vs non-obstructive disease. We hypothesized that pimobendan would be well tolerated in cats with CHF, with no difference in incidence of adverse effects between cats with and without OTO.

2 | MATERIALS AND METHODS

2.1 | Data collection

A retrospective medical record search was performed to identify cats who received at least 1 dose of oral pimobendan for treatment of CHF at Iowa State University Lloyd Veterinary Medical Center and North Carolina State Veterinary Hospital between 1 March 2004 and 1 March 2019. Cats were excluded if they were diagnosed with congenital heart disease or high-output heart failure secondary to severe anemia, or if an echocardiogram was not performed to characterize underlying cardiac disease. Cats were also excluded if they received a single oral dose of pimobendan before echocardiography and were subsequently diagnosed with noncardiac disease as the cause of their clinical signs.

Data obtained from medical records at the time of initial CHF diagnosis included date of CHF diagnosis; cat signalment; physical examination findings; blood pressure; echocardiographic data; electrocardiographic findings; serum blood urea nitrogen (BUN) and creatinine values; stage of chronic kidney disease based on a modification of the International Renal Interest Society (IRIS) guidelines (categorized as suggested by IRIS guidelines based on single serum creatinine value at time of CHF diagnosis, with no substaging attempted; http://www.iris-kidney.com/pdf/IRIS_Staging_of_CKD_modified_2019.pdf); presence or absence of arterial thromboembolism (ATE); cardiac disease diagnosis (see later); presence or absence of OTO (see later); presence of inciting event that might have precipitated CHF (anesthesia, fluid therapy, glucocorticoid administration, queening, ATE, or major environmental stressor); and the presence of concurrent systemic disease. Manifestation of CHF was recorded as presence or absence of pulmonary edema, pleural effusion, pericardial effusion, and ascites. Individual cats could have more than 1 manifestation of CHF; in these cases, cats were counted in each category of manifestation.

Cardiac disease diagnosis was based on echocardiographic findings as described by the ACVIM Consensus Panel.[6] Hypertrophic cardiomyopathy phenotype was defined by diastolic LV wall thickness > 6 mm. Hypertrophic cardiomyopathy phenotype in the presence of concurrent hyperthyroidism or systemic hypertension (systolic blood pressure > 180 mmHg) was classified as "HCM phenotype with hyperthyroidism" or "HCM phenotype with hypertension," respectively; cats with both hyperthyroidism and hypertension were placed in the former

(hyperthyroidism) category. Restrictive cardiomyopathy (RCM) was characterized by severe LA or biatrial dilation with evidence of LV diastolic dysfunction but normal LV wall thickness (< 6 mm). Dilated cardiomyopathy was characterized by LV dilation and systolic dysfunction. Acquired cardiomyopathies not conforming to these categories were classified as cardiomyopathy of nonspecific phenotype. Echocardiographic measurements of LV size, wall thickness, and fractional shortening were recorded from right parasternal short-axis M-mode views at the level of the chordae tendineae; LA to aorta ratio was recorded from 2-dimensional right parasternal short-axis views of the heart base using the Swedish method[18]; and LV outflow tract velocity was measured from left apical views optimized for the LV outflow tract and aorta.[19]

In cats with acquired heart disease, dynamic LV OTO was defined as the presence of turbulent flow on color Doppler in the LV outflow tract and a late-peaking continuous wave Doppler velocity > 1.9 m/s, with or without systolic anterior motion of the mitral valve.[13,20] Cats with dynamic midventricular LV obstruction were also classified as having OTO.[21] Hypertrophic cardiomyopathy phenotype with dynamic LV OTO was classified as HOCM phenotype. The presence of dynamic right ventricular OTO was not recorded and did not contribute to classification of obstructive cardiac disease.

Medication information obtained included date of first pimobendan administration; initial pimobendan dose and frequency; date of first oral furosemide administration; initial furosemide dose and frequency; other cardiac medications administered at initial diagnosis of CHF; occurrence and date of first dose escalation or dose decrease of pimobendan or furosemide, if applicable; final pimobendan dose and frequency at last follow-up; final furosemide dose and frequency at last follow-up; and all cardiac medications administered at time of last follow-up. Renal variables (BUN, creatinine, and IRIS stage) at time of last follow-up visit were also obtained.

Medical records and owner communication logs were examined for evidence of adverse events noted by owners after prescription of pimobendan, including (but not limited to) hyporexia/anorexia, vomiting, diarrhea, lethargy, weakness, or unusual agitation; and for hypotension and new or worsening arrhythmias detected at follow-up examinations.[5,9] These events were considered to be potential adverse effects related to pimobendan administration if they occurred within 45 days initial pimobendan administration and resolved with discontinuation of pimobendan. Adverse events were considered unrelated to pimobendan if the clinical signs coincided with either a relapse of CHF, addition of a different medication, or diet change; or if the clinical signs self-resolved with no change in pimobendan dose. If pimobendan was discontinued, date and reason for pimobendan discontinuation were recorded.

Long-term follow-up information included date and cause of death for cats that died during the study period, and date of last follow-up for cats alive at the end of the study period. Death was classified as cardiac for cats who died or were euthanized for worsening CHF or ATE, and for cats who died suddenly at home with no other obvious noncardiac cause.

2.2 | Statistical analysis

Statistical analysis was performed using commercially available software (SAS, version 9.4, Cary, NC; R software, version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria). Normality of data was assessed using the Shapiro-Wilk test. Continuous data are presented as mean ± SD for normally distributed data and as median(interquartile range, IQR) for nonnormally distributed data. Comparisons of variables between groups were performed using 2-sample t-tests for continuous normally distributed data, Wilcoxon rank-sum tests for continuous nonnormally distributed data, and Chi-square or Fisher exact tests for categorical variables. Statistical significance was set at $P < .05$ for all analyses. Cox proportional hazards regression analysis was performed to assess variables that were associated with all-cause or cardiac survival. Variables approaching significance ($P < .1$) in univariable analysis were subsequently entered into stepwise multivariable logistic regression analysis, with significance of the final models set at $P < .05$.

3 | RESULTS

3.1 | Study sample

A total of 260 cats were enrolled, comprising 85 cases from Iowa State University Lloyd Veterinary Medical Center and 175 cases from North Carolina State Veterinary Hospital. Sex distribution included 187 castrated males and 73 spayed females; median age was 10.0 (6.0) years. Breeds represented included domestic shorthair cats (n = 161), domestic longhair cats (51), Maine Coon (14), Siamese (9), Sphynx (4), Himalayan (3), Persian (3), Ragdoll (3), Bengal (2), Manx (2), Norwegian Forest cat (2), Burmese (1), Highland Lynx (1), Selkirk Rex (1), Singapura (1), Tonkinese (1), and Turkish Van (1).

Hypertrophic cardiomyopathy was the most common disease phenotype (n = 220). Across all disease groups, 57 cats (21.9%) had OTO. Eight cats categorized as having nonobstructive HCM phenotype at the time of CHF diagnosis had a history of OTO on previous echocardiograms. There was no difference between obstructive and nonobstructive disease groups in terms of incidence of hyperthyroidism (30/203 [14.8%] non-OTO, 3/57 [5%] OTO; $P = .10$) or hypertension (18/203 [8.9%] non-OTO, 2/57 [4%] OTO; $P = .37$). Cardiac disease diagnoses in the study sample, including number of cats with OTO by disease type, are shown in Table 1. Within each disease phenotype, there were no significant differences between study sites in terms of clinical, echocardiographic, treatment, or outcome variables.

3.2 | Clinical findings at time of CHF diagnosis

One hundred thirty-nine cats (53.5%) had concurrent noncardiovascular disease at the time of CHF diagnosis. The most common concurrent diseases reported in the medical record of >5 cats each were chronic kidney disease (n = 53), hyperthyroidism (30),

TABLE 1 Cardiomyopathy phenotype in 260 cats with congestive heart failure treated with pimobendan, 57 of which had outflow tract obstruction (OTO)

Disease phenotype	Number (%) of cats	Number (%) of cats with OTO
HCM	220 (84.6%)	56 (98.2%)
Primary HCM	120	0
Primary HOCM	51	51
Hyperthyroidism	30	3
Hypertension	18	2
Acromegaly	1	0
Nonspecific phenotype	20 (7.7%)	1 (1.8%)
RCM	12 (4.6%)	0 (0%)
DCM	8 (3.1%)	0 (0%)
Total	260 (100%)	57 (100%; 21.9% of all cats)

Abbreviations: DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; RCM, restrictive cardiomyopathy.

diabetes (19), anemia (22), feline asthma (16), chronic enteropathy/inflammatory bowel disease (9), and lymphoma (6). Concurrent systemic disease was more common in cats with nonobstructive heart disease (123/203, 60.6%) than in cats with obstructive disease (14/57, 25%; $P < .0001$).

Eighty-nine cats (34.2%) had 1 or more recent events recorded that might have contributed to precipitating CHF, including glucocorticoid administration (total n = 33; 18 injectable, 15 oral); concurrent ATE (25); fluid therapy (total n = 24; 12 intravenous, 11 subcutaneous, 1 blood transfusion); stressful life event (total n = 8; 4 escaped outdoors, 2 boarding kennel, 1 family move, 1 radioiodine treatment); and anesthesia (7). Some cats had more than 1 potential precipitating event. There was no difference between occurrence of presumed inciting events between nonobstructive (71/203, 35.0%) and obstructive (18/57, 32%) disease groups ($P = .75$).

Physical examination findings and manifestation of CHF for the study sample and by disease group (nonobstructive vs obstructive) are shown in Table 2. Murmurs were detected in a total of 127 cats and were localized as left parasternal (n = 80), left apical (9), right parasternal (9), and left basilar (2); 27 murmurs were not localized. Timing

TABLE 2 Clinical data at time of initial diagnosis of congestive heart failure for 260 cats treated with pimobendan, comparing 203 cats without and 57 cats with outflow tract obstruction

Variable	All cats	Nonobstructive	Obstructive	P value
Number of cats	260	203	57	...
Age (years)	10.0 (6.0)	10.8 (6.3)	8.9 (6.6)	**.0036***
Male (n, %)	187 (71.9%)	146 (71.9%)	41 (72%)	.13
Body weight (kg; n = 256)	5.1 (1.9)	5.0 (1.9)	5.1 (1.9)	.90
Rectal temperature (°F; n = 211)	100.5 (12.0)	100.5 (2.0)	100.2 (1.9)	.30
Heart rate (per minute; n = 259)	184 (50)	187 (48)	180 (40)	.29
Respiratory rate (per minute; n = 252)	60 (32)	60 (32)	60 (40)	.57
Blood pressure (mmHg; n = 211)	135 (33.5)	135 (30)	138.5 (45.5)	.68
Murmur (n, %; n = 258)	127 (49.2%)	76 (37.8%)	51 (89%)	**<.0001***
Gallop sound (n, %; n = 257)	66 (25.7%)	55 (27.5%)	11 (19%)	.23
Arrhythmia (n, %)	78 (30.0%)	68 (33.5%)	10 (18%)	**.02***
Pulmonary edema (n, %)	197 (75.8%)	144 (70.9%)	53 (93%)	**.0004***
Pleural effusion (n, %)	141 (54.2%)	122 (60.1%)	19 (33%)	**.0005***
Pericardial effusion (n, %)	86 (33.1%)	68 (33.5%)	18 (32%)	.87
Ascites (n, %)	27 (10.4%)	22 (10.8%)	5 (9%)	.81
Arterial thromboembolism (n, %)	25 (9.6%)	18 (8.9%)	7 (12%)	.45
Blood urea nitrogen (mg/dL, n = 242)	32.5 (18.75)	33 (19)	32 (16)	1.00
Creatinine (mg/dL, n = 243)	1.7 (0.8)	1.65 (0.8)	1.8 (0.7)	.27
Modified IRIS stage (n = 243)	I: 97 (39.9%) II: 129 (53.1%) III: 14 (55.8%) IV: 3 (1.2%)	I: 79 (41.5%) II: 97 (51.1%) III: 12 (6.3%) IV: 2 (1.1%)	I: 18 (34%) II: 32 (60%) III: 2 (4%) IV: 1 (12%)	.58

Note: Data are presented as median (IQR) for continuous nonnormally distributed data, and as number (percent) for categorical variables. Significant differences between groups ($P < .05$) are denoted in bold with an asterisk (*). The number of cats with data included is noted for variables with incomplete data sets. Modified IRIS staging was performed by applying IRIS cutoff guidelines to single serum creatinine value at time of CHF diagnosis, with no substaging attempted.

Abbreviation: IRIS, International Renal Interest Society.

was classified as systolic (n = 50) or not specified. Murmur intensity was graded as I/VI (n = 8), II/VI (42), III/VI (32), IV/VI (40), V/VI (2), or not recorded (3). One or more arrhythmias were diagnosed in 78 cats, characterized as ventricular ectopy (n = 48), atrial fibrillation (16), supraventricular ectopy (11), high-grade atrioventricular block (8), or atrial standstill (2). There were significant differences between nonobstructive and obstructive disease groups for cat age, presence of murmur, incidence of arrhythmia, and incidence of pulmonary edema or pleural effusion (see Table 2). When analysis was restricted to only primary HCM vs primary HOCM, the same patterns between groups were noted although the difference in incidence of pleural effusion was no longer statistically significant (P = .058).

Echocardiographic findings at time of CHF diagnosis are compared by disease groups in Table 3. Of cats diagnosed with dynamic LV OTO, 34/57 (60%) had systolic anterior motion of the mitral valve recorded. Mitral regurgitation was documented in a total of 194 cats (74.6%), graded as trace (n = 52), mild (118), moderate (22), and severe (2). Compared to cats with nonobstructive disease, cats with OTO had thicker LV walls, smaller LV lumen size, and higher fractional shortening (see Table 3). However, when restricting analysis to only cats with primary HCM vs HOCM, the only difference between groups was higher incidence of mitral regurgitation in the HOCM group (see Table 3).

3.3 | Cardiac medication prescribing practices

Pimobendan was prescribed on the day of CHF diagnosis in 200/260 (76.9%) cats, and was prescribed during hospitalization in 215/247 (87.0%) cats that survived to hospital discharge. Median (IQR) days between CHF diagnosis and pimobendan administration was 0 (0),

with a range of 0 to 2385 days. Pimobendan was most commonly initially prescribed at a dose of 1.25 mg PO q12h per cat, resulting in a median (IQR) total daily dose of 0.56 (0.2) mg/kg/day (range 0.12-1.74 mg/kg/day), with no difference in median dose administered between obstructive vs nonobstructive disease groups (P = .58; see Table 4). Dose or frequency of pimobendan was escalated at some point during the study period in 98 cats (37.6%), occurring a median of 39 days (range 3-978 days) from original diagnosis. Neither incidence of pimobendan dose increase (P = .76) nor timing from CHF diagnosis (P = .48) differed between disease groups (see Table 4). Pimobendan was administered for a median of 137 days per individual cat (range 0-2674 days), for a total pimobendan exposure of 73 232 cat-days (201 cat-years) for the entire study sample.

Furosemide was prescribed after the initial CHF episode in 231/247 (93.5%) cats surviving to hospital discharge. Median initial total daily dose of furosemide was 2.4 [1.7] mg/kg/day PO (range 0-7.86 mg/kg/day), with no difference between disease groups (P = .30; see Table 4). A minority of cats (16/246, 6.5%) had their CHF managed initially without administration of furosemide, using pimobendan with or without adjunctive vasodilators; these tended to be cats with concurrent severe chronic or acute kidney injury whose CHF manifested as cavitary effusion rather than pulmonary edema or cats whose CHF episode was precipitated by an external event. Dose or frequency of furosemide was increased at some point during the study period in 113 cats (43.5%) for intensification of CHF management, occurring a median of 27.5 days (range 3-973 days) from original CHF diagnosis. Neither incidence of furosemide dose increase (P = 1.00) nor timing from CHF diagnosis (P = .16) differed between obstructive versus nonobstructive disease groups. Dose of furosemide was decreased at some point during the study period in 71 cats (27.3%), occurring a median of 90 days (range 3-1078 days) from original CHF diagnosis, most commonly due

TABLE 3 Echocardiographic data at time of congestive heart failure diagnosis for 260 cats treated with pimobendan, comparing cats with vs without outflow tract obstruction and cats with primary HCM vs primary HOCM

Variable	Nonobstructive vs obstructive			Primary HCM vs HOCM		
	No OTO	OTO	P value	HCM	HOCM	P value
N	203	57	...	120	51	...
IVSd (cm)	0.56 ± 0.13	0.66 ± 0.15	**<.0001***	0.62 ± 0.12	0.67 ± 0.16	.08
LVIDd (cm)	1.58 (0.42)	1.45 (0.40)	**.0024***	1.48 (0.40)	1.40 (0.40)	.32
LVPWd (cm)	0.59 (0.27)	0.71 (0.28)	**<.0001***	0.70 ± 0.19	0.75 ± 0.17	.095
FS (%)	42.3 ± 15.4	48.2 ± 11.7	**.0022***	48.0 ± 12.9	48.3 ± 11.8	.86
LA : Ao	2.10 (0.59)	2.17 (0.63)	.69	2.01 (0.57)	2.21 (0.69)	.09
Mitral regurgitation (n, %)	146 (71.9%)	48 (84.2%)	.08	73/102 (71.6%)	44/51 (86.3%)	**.046***
Spontaneous echocontrast (n, %)	30 (14.9%)	11 (19.3%)	.42	17/102 (16.7%)	11/51 (21.6%)	.51
LA thrombus (n, %)	11 (5.5%)	2 (3.5%)	.74	6/102 (5.9%)	2/51 (3.9%)	.72

Note: Data are presented as mean ± SD for continuous normally distributed data, median (IQR) for continuous non-normally distributed data, and number (percent) for categorical variables. The number of cats with data included is noted as denominator values for variables with incomplete data sets. Significant differences between groups (P < .05) are denoted in bold and with an asterisk (*).

Abbreviations: Ao, aorta; FS, fractional shortening; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; IVSd, interventricular septal thickness in diastole; LA, left atrium; LVIDd, left ventricular internal diameter in diastole; LVPWd, left ventricular posterior wall thickness in diastole; OTO, outflow tract obstruction.

TABLE 4 Drug dosage information and follow-up data for 260 cats treated with pimobendan, comparing 203 cats without and 57 cats with outflow tract obstruction

Variable	All cats	Nonobstructive	Obstructive	P value
Number of cats	260	203	57	...
Initial pimobendan dose (mg/kg/day)	0.56 (0.20)	0.55 (0.21)	0.56 (0.17)	.58
Final pimobendan dose (mg/kg/day)	0.61 (0.40)	0.61 (0.43)	0.62 (0.38)	.76
Pimobendan dose increase (n, %)	98 (37.7%)	78 (38.4%)	20 (35%)	.76
Initial furosemide dose (mg/kg/day)	2.44 (1.74)	2.47 (1.68)	2.31 (2.46)	.30
Final furosemide dose (mg/kg/day)	2.57 (3.27)	2.57 (3.1)	2.46 (4.9)	.94
Furosemide dose increase (n, %)	113 (43.5%)	88 (43.3%)	25 (44%)	1.00
Furosemide dose decrease (n, %)	71 (27.3%)	57 (28.1%)	14 (25%)	.74
Blood urea nitrogen at last follow-up (mg/dL, n = 215)	35 (19.5)	35 (19.5)	36 (21)	.98
Creatinine at last follow-up (mg/dL, n = 218)	1.8 (1.0)	1.7 (0.9)	1.95 (1.0)	**.04***
Modified IRIS stage at last follow-up (n = 218)	I: 79 (36.2%) II: 106 (48.6%) III: 18 (8.3%) IV: 15 (6.9%)	I: 67 (40.3%) II: 74 (44.6%) III: 13 (7.8%) IV: 12 (7.2%)	I: 12 (23%) II: 32 (62%) III: 5 (10%) IV: 3 (6%)	.85
Incidence of all-cause death (n, %)	152 (58.5%)	117 (57.6%)	35 (61%)	.21
Incidence of cardiac death (n, %; n = 246)	105 (42.7%)	82 (42.3%)	23 (44%)	.87
Survival time (all deceased cats, n = 117)	150.5 (408)	144 (352)	208 (449)	.25
Follow-up time (alive or lost to follow-up, n = 108)	227 (539)	195 (546)	328 (502)	.32
Survival time (cardiac death only, n = 105)	152 (333)	143.5 (317)	240 (435)	.09

Note: Data are presented as median (IQR) for continuous nonnormally distributed data, and as number (percent) for categorical variables. Significant differences between groups (P < .05) are denoted in bold with an asterisk (*). The number of cats with data included is noted for variables with incomplete data sets. Modified IRIS staging was performed by applying IRIS cutoff guidelines to single serum creatinine value at time of CHF diagnosis, with no substaging attempted.

Abbreviation: IRIS, International Renal Interest Society.

to new or worsening azotemia. Neither incidence of furosemide dose decrease (P = .74) nor timing from CHF diagnosis (P = .84) differed between disease groups (see Table 4).

The final follow-up visit wherein all medication doses were recorded occurred a median of 93 (347) days after initial CHF visit. Medication dosing information and renal variables at this visit are depicted in Table 4. Final total daily dose of pimobendan was 0.61 (0.40) mg/kg/day (range 0-4.26 mg/kg/day), while final total daily dose of furosemide was 2.57 (3.27) mg/kg/day (range 0-14.3 mg/kg/day). Final creatinine value in the obstructive disease group was higher than in the nonobstructive group; however, when analysis was restricted to primary HCM and HOCM only, there was no difference in final creatinine value between HOCM (1.95 [1.0] mg/dL) and HCM (1.8 [0.95] mg/dL) cats (P = .39).

Besides furosemide and pimobendan, the most commonly prescribed cardiac medications in the study sample are listed in Table 5, with comparisons between initial CHF visit and final follow-up visit. Prescription of additional cardiac medications did not differ between disease groups except for atenolol, being administered at the initial CHF visit in 14 (6.9%) nonobstructive cats and 11 (19%) obstructive cats (P = .0094). At the final follow-up visit, the proportion of cats receiving atenolol no longer differed between nonobstructive (14, 6.9%) and obstructive (6, 11%) cats (P = .40).

TABLE 5 Oral medications prescribed at initial diagnosis of congestive heart failure compared to final follow-up visit in 247 cats treated with pimobendan that survived to hospital discharge

Medication	Prescribed at initial CHF diagnosis (n, %)	Receiving at final follow-up visit (n, %)
Pimobendan	215 (87.0%)	239 (96.8%)
Furosemide	231 (93.5%)	190 (76.9%)
Torsemide	0 (0%)	18 (7.3%)
Enalapril or benazepril	180 (72.9%)	172 (69.6%)
Clopidogrel	204 (82.6%)	191 (77.3%)
Aspirin	20 (8.1%)	15 (6.1%)
Dalteparin	32 (13.0%)	40 (16.2%)
Apixaban	3 (1.2%)	4 (1.6%)
Spironolactone	10 (4.0%)	14 (5.7%)
Atenolol	25 (10.1%)	20 (8.1%)
Diltiazem	12 (4.9%)	11 (4.5%)
Sotalol	5 (2.0%)	4 (1.6%)
Amlodipine	14 (5.7%)	12 (4.9%)
Sildenafil	1 (0.4%)	5 (2.0%)

3.4 | Adverse events and adverse effects

Adverse events that might or might not have been drug-related were reported in a total of 55 cats (21.2%) during the study period, including 43/203 (21.2%) nonobstructive cats and 12/57 (21%) cats with obstructive disease. Adverse events occurred a median of 44 days (range 1-1408) from onset of CHF. Neither incidence of adverse events (P = .85) nor timing from CHF diagnosis (P = .95) differed between nonobstructive and obstructive disease groups. The most common adverse events included hyporexia/anorexia (n = 23, 5 of which were also reported to be lethargic and 2 of which were also vomiting), vomiting (23, 4 of which also had diarrhea and 2 of which were also hyporexic/anorexic), diarrhea (10, 4 of which also had vomiting), new onset ventricular arrhythmias (3), and subclinical hypotension (2). The majority of adverse events were considered unrelated to pimobendan administration, because the adverse event either occurred >45 days after initiation of pimobendan (n = 25), coincided with addition of a new medication (other than pimobendan) or diet change (7), coincided with a relapse of CHF and resolved with intensified treatment of CHF (6), was attributed to concurrent noncardiac disease (3), or had been reported before pimobendan prescription (2).

Twelve cats (4.6%), including 11 (5.4%) cats with nonobstructive disease and 1 (2%) cat with obstructive disease, were reported to experience adverse effects considered to be potentially attributable to pimobendan based on patterns of timing and resolution. These adverse effects occurred a median of 10 days (range 1-40) after pimobendan initiation, and consisted of hyporexia/anorexia (7 cats, 1 of which was also lethargic and 2 of which also had vomiting), vomiting (6 cats, 2 of which also had hyporexia/anorexia), and subclinical hypotension (1 cat). Incidence of adverse effects did not differ between disease groups (P = .70).

Pimobendan was discontinued during the study period in 17 cats (6.5%), including 11/203 (5.4%) cats with nonobstructive disease and 6/57 (11%) cats with obstructive disease. Discontinuation of pimobendan occurred a median of 141 days after initiation of pimobendan (range 2-1078 days). There was no difference in incidence of discontinuation (P = 1.00) or time to discontinuation (P = .48) between disease groups. The most common reason for discontinuation of pimobendan was that the cat's CHF had resolved and the underlying structural heart disease had improved to the point where ongoing therapy for CHF was considered no longer necessary (n = 11). In all of these cases, diuretic therapy was also discontinued. Underlying heart diseases originally diagnosed in these 11 cats included HCM phenotype with hypertension (2) or hyperthyroidism (1), and primary HCM (5) or HOCM (3). Four of these 11 cats (36%) had 1 or more inciting events potentially precipitating their initial CHF episodes, including glucocorticoid administration (n = 2) and escape outdoors (2). Other reasons for discontinuation of pimobendan included cat or owner noncompliance (n = 2) and adverse effects (n = 4).

Pimobendan was discontinued due to adverse effects in a total of 4/260 cats (1.5%), including 3 cats with nonobstructive disease (1.5%) and 1 cat with obstructive disease (2%). There was no difference in incidence of pimobendan discontinuation due to adverse effects between groups (P = 1.00). Two cats with nonobstructive cardiomyopathy (HCM and nonspecific phenotype) receiving pimobendan at 0.77 and 0.94 mg/kg/day discontinued pimobendan due to development of vomiting 2 and 17 days after initiation of the drug, respectively. These cats were both still alive at last follow-up, 246 and 1091 days after initial CHF diagnosis. Another cat with HCM and ATE receiving pimobendan at 0.74 mg/kg/day discontinued the drug 40 days after initiation because owners perceived that the cat developed lethargy and nausea after each pimobendan administration (this cat received all medications through an esophagostomy tube). This cat was euthanized for recurrent ATE 87 days after initial CHF diagnosis. A single cat with obstructive cardiomyopathy (HOCM) had pimobendan discontinued due to documentation of subclinical hypotension. This cat had improved clinically during initial hospitalization and treatment for CHF, and was discharged with furosemide, pimobendan (0.33 mg/kg/day), enalapril, aspirin, and dalteparin. At a recheck examination 2 days later, the cat was feeling clinically well, but noninvasive blood pressure was measured at 80 mmHg. Furosemide dose was decreased and both pimobendan and enalapril were discontinued. This cat was euthanized for renal lymphoma 240 days after initial CHF diagnosis.

3.5 | Outcome and survival

One hundred fifty-two cats (58.5%) died during the study period, comprising 117 cats with nonobstructive disease (57.6%) and 35 cats with obstructive disease (61%). The majority (105/152, 69.1%) died of cardiac causes. Incidence of all-cause death (P = .21) and cardiac death (P = .87) did not differ between obstructive and nonobstructive disease groups. Of cats experiencing cardiac death, the majority (64/105, 61.0%) died or were euthanized for CHF, including 5 cats that were euthanized and 2 who had cardiopulmonary arrest during hospitalization for their initial CHF presentation. Of the 57 cats euthanized after hospital discharge for relapse or recurrence of CHF, 9 cases (16%) also had chronic kidney disease or acute kidney injury that limited dose escalation of furosemide and contributed to the decision to euthanize. Twenty-four cats (22.9% of cardiac death) were euthanized for ATE, 6 of which were euthanized prior to hospital discharge. An additional 17 cats (16.2% of cardiac death) died suddenly at home. Of cats in this study dying of known noncardiac causes, 12/47 (26%) were euthanized for kidney disease (acute or chronic).

Median survival time after CHF diagnosis for deceased cats was 150.5 days (range 0-2444) and did not differ between cats with obstructive vs nonobstructive disease (P = .25; see Table 4). One hundred eight cats were alive at the end of the study period or lost to follow-up, with a median follow-up time of 227 days (range 0-2674) that did not differ between study groups (P = .32). When analysis was restricted to only cats with primary HCM vs HOCM, median survival time also did not differ between groups (271 days overall; 246 days for HCM, 329 days for HOCM; P = .96). Median survival time was significantly shorter for cats experiencing cardiac death (median

101 days) compared to noncardiac death (median 1415 days; $P < .0001$). Variables significantly predictive of all-cause and cardiac death in multivariable analysis are shown in Table 6.

4 | DISCUSSION

This study reports retrospective outcomes of pimobendan treatment for CHF in a large group of cats (n = 260), including a large group of cats with OTO (n = 57). Pimobendan was safe and well tolerated in this sample of cats, with 4.6% of cats having adverse effects potentially related to pimobendan and 1.5% of cats having pimobendan therapy discontinued due to adverse effects, with no differences between cats with obstructive versus nonobstructive disease. These findings support our hypothesis and add to existing literature demonstrating that pimobendan is well tolerated in cats with CHF regardless of the presence of OTO.[16] These results further suggest that pimobendan can be safely given as a therapy for CHF without a specific phenotypic heart disease diagnosis on echocardiogram.

The most common adverse effects reported in this cat sample were hyporexia/anorexia (2.7%) and vomiting (2.3%). Incidence and types of adverse effects reported during the study period are similar to those in other retrospective studies of pimobendan use in cats. Adverse effects in 5/170 (2.9%) cats receiving pimobendan are described as unusual agitation (n = 2), anorexia (1), vomiting (1), and constipation (1).[15] This study included 4 cats with dynamic LV OTO,

none of which were among the cats showing adverse effects. Two additional retrospective studies report no adverse effects in samples of cats receiving pimobendan (0/16 cats[14] and 0/27 cats[16]).

In another previous study of 27 cats receiving pimobendan, 1 cat (4%) with LV OTO had an adverse effect. This cat was diagnosed with complex congenital heart disease (mitral valve dysplasia and ventricular septal defect) including systolic anterior motion of the mitral valve, and was reported to experience acute hypotension (systolic blood pressure 60 mmHg) and tachycardia (240 bpm) after a single dose of pimobendan PO. In the present study, no cats were reported to experience acute hemodynamic adverse effects or clinical signs of hypotension after administration of pimobendan orally. A single cat with HOCM had pimobendan discontinued due to subclinical hypotension detected at a routine follow-up visit after initial hospitalization and treatment for CHF. This cat was also receiving furosemide and enalapril, and all drugs were started concurrently; at the time of hypotension diagnosis, enalapril and pimobendan were both discontinued and the dose of furosemide was reduced. Therefore, it is difficult to know whether subclinical hypotension in this case was related to pimobendan vs other medical therapy. Recheck of blood pressure after starting CHF therapy is routine practice in both study institutions, providing an opportunity to detect hypotension even in the absence of clinical signs. However, it is possible that some cases of subclinical hypotension could have been missed if cats did not have blood pressure documented after starting pimobendan. The present study demonstrated no difference in incidence of adverse effects between cats

TABLE 6 Final model of the Cox proportional hazards multivariable analysis of all-cause and cardiac death in 260 cats with congestive heart failure who received pimobendan, 105 of whom died of cardiac causes

Variable	Hazard ratio	95% confidence interval of hazard ratio	P value
All-cause death			
Age	1.090	1.039-1.142	.0004
LVPWd	0.185	0.064-0.531	.0017
FS	0.981	0.969-0.995	.0056
Final BUN	1.004	1.000-1.008	.0291
Initial modified IRIS stage III	3.291	1.443-7.507	.0046
Cardiac death			
Sex (male)	0.185	0.087-0.392	<.0001
Temperature	0.684	0.560-0.836	.0002
Murmur present	0.252	0.127-0.502	<.0001
Initial creatinine	2.395	1.557-3.684	<.0001
IVSd	0.051	0.005-0.519	.0120
LVIDd	3.798	1.374-10.498	.0101
PCEFF present	2.355	1.131-4.904	.0220
ATE present	7.736	3.35-17.999	<.0001

Note: A hazard ratio > 1.0 indicates that presence (categorical variables) or increasing values (continuous variables) of that variable were associated with increased hazard (increased likelihood of death), while hazard ratios <1.0 indicate that presence or increasing values of that variable conferred a protective effect (decreased likelihood of death). Modified IRIS staging was performed by applying IRIS cutoff guidelines to single serum creatinine value at time of CHF diagnosis, with no substaging attempted.

Abbreviations: ATE, arterial thromboembolism; BUN, blood urea nitrogen; FS, left ventricular fractional shortening; IRIS, International Renal Interest Society; IVSd, interventricular septal wall thickness in diastole; LVIDd, left ventricular internal diameter in diastole; PCEFF, pericardial effusion.

with obstructive and nonobstructive heart disease, and no evidence to suggest a clinically relevant worsening of OTO with pimobendan.

Two cats in this study without previously recorded arrhythmias were diagnosed with ventricular ectopy after pimobendan administration. However, intermittent arrhythmias prior to pimobendan administration could certainly have been missed; diagnostic rhythm assessment was not standardized and Holter monitoring was not performed in any cats, making it difficult to rule out the possibility that ventricular ectopy predated pimobendan administration in these cases.[22] Pimobendan is not currently labeled for use in human heart disease in the United States based on a clinical trial suggesting increased death and a concern for proarrhythmic effects for pimobendan compared to placebo.[23] However, Holter-based studies have failed to demonstrate a proarrhythmic effect in small-breed dogs.[24]

The dose of pimobendan used in this study (typically 1.25 mg per cat PO q12h; median initial total daily dose in this study 0.55 mg/kg/day) was close to the recommended label dose of pimobendan in dogs (0.25-0.3 mg/kg PO q12h; total daily dose 0.5-0.6 mg/kg/day). Pharmacokinetic studies of pimobendan in healthy cats have demonstrated that pimobendan has a substantially higher maximal drug plasma concentration and longer elimination half-life in cats compared to dogs,[25] but decreased conversion to the active metabolite O-desmethylpimobendan.[26] Therefore, although the ideal dose of pimobendan in cats remains unknown, the use of the canine dose seems rational given the existing pharmacokinetic and pharmacodynamics data. Pimobendan dose was escalated in approximately one-third of cats in the present study (with a median final dose of 0.61 mg/kg/day) with no adverse effects reported in association with dose escalation, suggesting that pimobendan has at least a reasonable margin of safety in cats.

Although the focus of this study was safety and tolerability of pimobendan, the data also provided clinical and outcome data for a large group of cats with CHF. Overall demographic data were similar to previous studies of HCM in cats.[27,28] The only clinical or physical examination variables that differed between obstructive and nonobstructive groups were that cats with OTO were younger, more likely to have a heart murmur, and less likely to have an arrhythmia; on echocardiogram, cats with OTO had more severe LV hypertrophy, smaller LV lumen size, and higher LV fractional shortening values. These differences are all logical given the definitions of each disease phenotype and the fact that a dynamic LV OTO is more likely to occur in cats with more severe hypertrophy, especially if the hypertrophy occurs in the region of the basilar interventricular septum.[29] Younger age of cats with OTO could be explained by 2 factors: cats with OTO might be diagnosed with heart disease at a younger age due to the presence of a heart murmur; and older cats with HCM phenotype secondary to hypertension or hyperthyroidism were typically nonobstructive. Other clinical and echocardiographic variables including heart rate, respiratory rate, presence of gallop sound, renal values, LA size, and presence of ATE did not differ between groups.

Obstructive and nonobstructive groups differed in their manifestations of CHF, with OTO cats more likely to develop pulmonary edema and nonobstructive cats more likely to develop pleural effusion. It is well recognized that cats with structural heart disease that is predominantly phenotypically left-sided can develop either pulmonary edema, pleural effusion, or both. A number of studies have reported the relative frequency of different manifestations of CHF in cats,[30-32] reporting incidence of pleural effusion between 51% and 79% and incidence of pulmonary edema between 49% and 85%; however, these studies do not separate manifestation of CHF by heart disease diagnosis or presence of OTO. Two previous retrospective studies suggested certain echocardiographic characteristics that might be predictive of pleural effusion in cats with CHF, including increased right ventricular size, decreased LA function, and decreased LV and right ventricular longitudinal systolic function.[11,33] Whether presence or absence of OTO correlated with pleural effusion or these predictive echocardiographic measures was not reported in these studies. LA function, right heart dimensions, and longitudinal systolic function were not evaluated in the present retrospective study; therefore, it is impossible to know whether the presence of OTO was independently predictive of pleural effusion. Further study is needed to explore whether the association between OTO and pulmonary edema (or nonobstructive disease and pleural effusion) is truly causative, or simply a correlation between the presence or absence of OTO and other echocardiographic measures.

Median survival time after initiation of pimobendan in this study (151 days) was comparable to other retrospective studies of cats receiving pimobendan for a variety of cardiomyopathies, with median survival in previous reports ranging from 49 to 167 days.[12,14,15] Direct comparisons between these investigations are complicated because these studies enrolled variable numbers of cats with cardiomyopathies (particularly DCM and RCM) considered to have poorer prognosis.[34,35] When considering only cats with primary HCM or HOCM, median survival time in the present study (271 days) was higher than that of some previous reports involving cats not treated with pimobendan (92-194 days),[16,36,37] but lower than that of a small cohort of 27 pimobendan-treated cats (626 days).[16] Again, direct comparisons between these retrospective studies are inherently challenging given differences in inclusion criteria and ancillary treatments for CHF; no conclusions regarding efficacy or survival benefit of pimobendan can be drawn from this study.

Median survival time was numerically higher for cats with OTO (median survival 208 days) compared to nonobstructive disease (median survival 144 days), but this difference was not statistically significant. Increased survival in HOCM compared to HCM has been previously reported in some studies[27,32] and might be related to younger age of HOCM cats at diagnosis. Lower incidence of concurrent systemic disease in cats with obstructive disease in this study (25% in cats with OTO vs 61% in nonobstructive cats) might also have contributed to longer survival times in this group. Death in the present study sample was predominantly cardiac (69%), with distribution of specific cause of cardiac death (61% CHF, 23% ATE, 16% sudden cardiac death) similar to previous reports.[27,28,36,38] Clinical and echocardiographic predictors of either all-cause or cardiac death in multivariable analysis were generally consistent with previous

reports[27,28,32,37] and included increased age, decreased rectal temperature, lack of heart murmur, presence of ATE, increased LVIDd, and decreased indices of LV systolic function. Increased LV wall thickness was actually associated with a *decreased* risk of all-cause or cardiac death, contrary to previous studies of feline HCM;[28,32] however, this likely reflects the inclusion of cats with other cardiomyopathy phenotypes defined by normal to reduced LV wall thickness (RCM, DCM) and associated with poorer prognoses.[14,34,35] Interestingly, male cats had a lower risk of death compared to female cats in this group. Although sex has not been shown to be a prognostic factor in previous descriptions of feline cardiomyopathy, this might be due to differences in sex distribution among disease phenotypes with differing prognoses.

An interesting finding of the present report is the clinical relevance of azotemia and chronic kidney disease in management of cats with CHF. Median creatinine values at CHF diagnosis (1.7 mg/dL) and at final follow-up (1.8 mg/dL) suggest that the "typical" cat in this study had IRIS stage II chronic kidney disease. Concurrent kidney disease affected treatment and outcome in many cases: 27% of cats had furosemide dose decreased at some point during the study, typically due to worsening azotemia. Among cats euthanized for refractory CHF, 16% had azotemia that limited further dose escalation of furosemide, and of cats in this study dying of noncardiac disease, 26% were euthanized for kidney disease (acute or chronic). Indeed, multivariable survival analysis revealed that final BUN and IRIS stage III chronic kidney disease were independent predictors of all-cause death, and initial creatinine was predictive of cardiac death. These findings underscore the role of cardiovascular-renal axis disorders[39] in management of CHF in cats.

A relevant fraction of cats in the present study (34%) had an antecedent event that might have precipitated CHF, including ATE, parenteral fluid administration, glucocorticoid administration, recent anesthesia, queening, or other stressors. A previous study of feline CHF[27] reported even higher incidence (51%) but similar types of precipitating events, although ATE was not included as a precipitating stressor in that study. Antecedent events were also reported before CHF in 29% of cats diagnosed with HCM and 71% of cats with CHF associated with transient myocardial thickening, thought to be a temporary myocardial disease of cats that can cause reversible CHF.[40] In the present study, 11 cats had cardiac disease that was ultimately reversible to a degree that cats were able to discontinue furosemide and pimobendan treatment; indeed, this was the most common reason for discontinuation of pimobendan in this study group. Of those 11 cats, 2 had cardiac disease presumed to be secondary to a systemic disease (anemia, systemic hypertension, or hyperthyroidism) and thus had a potentially reversible phenotype with treatment of underlying disease. The remaining 8 cats (4 of which had precipitating stressors) were diagnosed with HCM or HOCM phenotype at the time of CHF, suggesting that these 8 cats might have actually had transient myocardial thickening rather than primary myocardial disease.

This study had several limitations related to its retrospective nature. Most importantly, all cats in this study received pimobendan; there was no control group receiving placebo or alternate treatment.

This precludes any assessment of drug efficacy, and also limits the ability to truly characterize adverse effects as drug-related. Second, definitions of disease phenotypes in feline cardiomyopathy is inherently difficult. The authors used recent consensus guidelines[6] and chose to separate disease groups based on the presence or absence of OTO, instead of limiting the study to HCM vs HOCM. The goal of this approach was to include cats with OTO and disease phenotypes other than HCM; however, this approach limits disease-specific comparisons for other clinical variables. Phenotypic classification was also limited by difficulty assessing diastolic function due to summation of E and A waves on transmitral inflow and tissue Doppler imaging at typical feline heart rates. For purposes of IRIS staging, creatinine values at CHF diagnosis and final follow-up were presumed to reflect stable renal function, while in reality, creatinine values in these cats might have reflected a combination of chronic kidney disease and acute kidney injury. Another limitation of this retrospective study is that case management and drug prescribing practices might have differed between clinicians or institutions and might have changed over time throughout the study period. As discussed earlier, the medical record review might have missed adverse events that were either not reported by owners or occurred after the last follow-up, and adverse events that were not specifically looked for (such as development of a subclinical hepatopathy) would not be identified.

Results of this study suggest that pimobendan was safe and well tolerated in a large group of cats with CHF secondary to various underlying cardiac disease phenotypes, with no increased risk of adverse effects for cats with obstructive disease. Further long-term prospective studies will be needed to determine potential effects of pimobendan on quality of life and survival in cats with CHF.

CONFLICT OF INTEREST DECLARATION
Drs. Ward, Kussin, and Tropf have no relevant disclosures. Drs. DeFrancesco, Tou, and Keene have received consulting fees or honoraria from Boehringer Ingelheim Vetmedica, Inc. and CEVA Animal Health.

OFF-LABEL ANTIMICROBIAL DECLARATION
Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION
Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION
Authors declare human ethics approval was not needed for this study.

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